Response to Federal Register Public Comments on Methyl Ethyl Ketone 11/2003

Comments from George V. Alexeeff, Ph.D., D.A.B.T.

Comment:

I would like to raise concerns regarding the AEGL-1 and 2 values recommended by the AEGL Committee for Methyl Ethyl Ketone.

The AEGL-1 is based on human data indicating irritation was objectionable at 350 ppm, and was considered acceptable at 200 ppm following 3-5 minutes of exposure. Another study indicated the absence of objectionable effects after 4 hours of exposure to 200 ppm. The document further discusses the absence of neurobehavioral effects following a 4-hour exposure to 200 ppm. Finally, the document also indicates reports of slight irritation occurred at 100 ppm. Based on these and some supporting studies the document concludes: "therefore, 100 ppm was selected as the threshold for sensory irritation." I suggest the following modifications in this approach that would change the AEGL-1 value slightly, but would be more scientifically defensible:

- Describe the 200 ppm level as the NOAEL for AEGL-1 effects of objectionable irritation and neurobehavioral effects.
- Describe the 350 ppm level as the LOAEL for the AEGL-1 effects of objectionable irritation of the eyes, nose and throat.
- These two changes would be consistent with the standard operating procedures regarding description of the toxicological endpoint of concern.
- If 200 ppm is chosen as the starting point, I suggest that an UF of 3 would be consistent with the committee's previous practice. This would result in an AEGL of 67 ppm, close to the current 100 ppm value. Choice of the 67 ppm value would also address any concerns about the irritation observed in some studies at 100 ppm. Since the endpoint is objectionable irritation, there is no clear justification in the document that there would be no variation in response in the human population.
- The Endpoint described in the Summary Table (page viii, line 6), that is "Threshold for sensory irritation in humans" would be improved if it were revised to "NOAEL for objectionable irritation." Similar changes should occur in the Executive Summary, and summary tables, and derivation section and in the appendix calculations.

Response:

The National Advisory Committee (NAC) for AEGLs passed the values for methyl ethyl ketone (MEK) in December 2001. Values are revisited by the NAC when new data are made available or if there is an obvious misinterpretation of the data. The comments do not address either of these factors.

The 200 ppm level is indeed a NOAEL for AEGL-1 effects of objectionable irritation and neurobehavioral effects. In fact, it is a NOAEL for any effect, and thus is below the definition of the AEGL-1. Newly published studies support 200 ppm as a NOAEL for irritation; these studies have been incorporated into the current TSD. The

recent clinical studies with over 100 healthy male and female subjects and 12 subjects with multiple chemical sensitivity support the use of an intraspecies uncertainty factor of 1. In light of the new data and the previous well-conducted clinical studies of Dick et al. (1984, 1988, 1999, 1992), the AEGL-1 which is presently based on a 1943 study with no analytically-determined concentrations (Nelson et al. 1943) should indeed be revisited.

The editorial comments are appreciated and will be incorporated into the TSD where appropriate. However, we remind the commenter that the phrase, "AEGL values represent *threshold* levels for the general public" appears in the Preface of every TSD.

Comment:

The AEGL 2 rationale is based on the chronic study of Cavendar et al. (1983) in which rats were exposed to 5,000 ppm for 5 days/week for 90 days. The document states: "the 5000 ppm concentration is close to the threshold for neurotoxicity as evidenced by somnolence in another repeated exposure study in which rats were exposed to 6,000 ppm for several weeks (Altenkirch et al. 1978)." If these studies are used as the basis for developing the AEGL-2, I suggest that the document clearly state that:

- The 5000 ppm level is the NOAEL for the AEGL-2 effects of narcosis and that 6000 ppm is the LOAEL for narcosis. The current statement that 5000 ppm is the threshold for narcosis is unclear.

This lack of clarity is exemplified by the statement (page 30, line 6): "Because of the mild endpoint and the nature of the key study and because rodents have a higher respiratory rate and cardiac output than humans, resulting in more rapid uptake of chemical, no interspecies uncertainty factor was applied." The AEGL-2 should not be based on a "mild endpoint." The document must be referring to the AEGL-1 effects that are occurring at the AEGL-2 NOAEL. Because the document did not clearly specify the AEGL-2 NOAEL and LOAEL, as described in the standard operating procedures, the endpoint discussed appears to be unclear. Based on all previous committee discussion, narcosis is not considered a mild endpoint and is considered to be a relevant AEGL-2 effect.

The AEGL-2 does not use an interspecies uncertainty factor, but instead states: "because rodents have a higher respiratory rate and cardiac output than humans, resulting in more rapid uptake of chemical, no interspecies uncertainty factor was applied." No documentation is provided in the document that shows rodents are more sensitive than humans to the AEGL-2 effects. Instead, one of the few human studies addressing this topic, Smith and Mayers (1944) suggests that humans could be more sensitive than rodents since fainting spells were reported at levels close to 600 ppm. Generally pharmacokinetic arguments are justified in reducing an uncertainty factor from 10 to 3. However, since some of the interspecies uncertainty is due to the pharmacodynamics of the response, interspecies uncertainty remains. For the chemical tetrafluoroethane (Volume 2), the use of an interspecies uncertainty factor 3 for narcosis as well as an intraspecies uncertainty factor of 3 was used as supporting documentation. For the chemical 1,1-dichloro-1-fluoroethane (Volume 2), the use of an interspecies uncertainty factor 3 for narcosis as well as an intraspecies uncertainty factor of 3 was also used as supporting

documentation. Thus, previous AEGL values adopted by the committee and the National Research Council appear to support the use of an interspecies uncertainty factor 3 for narcosis as well as an intraspecies uncertainty factor of 3, for a total uncertainty factor of 10. This would reduce the AEGL-2 values to 500 ppm.

I request that the Committee consider these recommendations and revise the AEGL documents accordingly.

Response:

The document will be rewritten to state that 5000 ppm is the NOAEL for narcosis. The term, mild endpoint, will be deleted. It is not clear that 6000 ppm is a LOAEL for narcosis in the rat as the exposures were repeated and the first day on which somnolence was observed was not clearly stated. Furthermore, this effect was "mild" in rodents compared with another chemical tested at the same time. Because rodents have higher respiratory rates and cardiac output (the two primary determinants of systemic uptake of volatile chemicals), than primates, the National Academy of Sciences (NAS) has instructed us to use an uncertainty factor of 1, unless there are data to the contrary. Such data (more rapid uptake and higher blood steady-state concentrations for rodents compared with humans) are available and have been incorporated into the rewritten TSD.

The Smith and Mayers (1944) study is old and has many uncertainties. In addition to inhalation exposures, the workers were dermally exposed as evidenced by "disabling dermatoses." The authors reported that the workers tended to wash their hands in the solvent. The analytical method used to measure atmospheric concentrations in 1944 was not provided. Studies with such shortcomings have been rejected by the NAS as the basis for effects.

Neither tetrafluoroethane nor 1,1-dichloro-1-fluoroethane (NRC 2001, Volume 2) induce narcosis. They are inert gases. It is true that we generally use an intraspecies uncertainty factor of 3 for narcosis. Unfortunately, the use of an interspecies uncertainty factor of 3 was necessary to lower no-effect concentrations for these inert chemicals to levels that would be supportive of the chosen AEGL-1 value. This was not the reasoning for the interspecies uncertainty factor of 1 for the AEGL-2 of MEK. The AEGL-2 was based on a *no-effect level in a subchronic study* with rats (Cavendar 1983).

Comments from John S. Morawetz:

Comments:

I would like to raise concerns regarding the AEGL-2 values recommended by the AEGL Committee for Methyl Ethyl Ketone (MEK).

Need for Interspecies Uncertainty Factor

The current AEGL 2 rationale is based on the chronic study of Cavendar, 1983 in which rats were exposed to 5,000 ppm for 90 days. The committee did not use any interspecies uncertainty factor because this was a no-effect repeated-exposure study but the rats in the Altenkirch, 6,000 ppm study, developed somnolence within 5 to 10 minutes. In addition, the TSD notes that this study was begun at 10,000 ppm but lowered to 6,000 within a few days due to "severe irritation of the respiratory tract".

Alternatively, the 5,000 ppm Cavendar exposure should be considered a 10 minute threshold for AEGL-2 due to both rapid somnolence (a surrogate for difficulty to escape) and severe enough respiratory irritation at higher exposures to force lower study exposures. If the repeated exposure is then not present, an interspecies uncertainty factor of 3 should be applied for AEGL-2 values while starting with the 5,000 ppm exposure. With the intraspecies uncertainty factor of 3 the resulting levels would be supported by Smith and Mayers which found two cases of fainting at exposures of up to 600 ppm (likely area samples of unknown duration). This study also found significant numbness in the legs and "a tendency for them to suddenly give way under him", symptoms which might cause difficulty in escape.

Response:
See previous answer concerning use of an interspecies uncertainty factor of 1. In addition, the Smith and Mayers (1944) study is poor support for a value of 500 ppm for the reasons cited above (dermal uptake, repeated exposures , analytical methodology not specified) as well as the fact that (as John states) these were probably area samples of unknown duration. Furthermore, the numbness in the legs is a result of chronic exposure, not a single exposure.

Comments from Mary Lee Hultin
Toxicology Specialist
Air Quality Division
Michigan Department of Environmental Quality

Comment:
AEGL-1 value:
While selection of 100 ppm as the threshold for sensory irritation appears to be the prudent and conservative choice for derivation of the AEGL-1, questions still remain as to the most germane principal study and the use of uncertainty factors. According to the documentation provided with the California Acute Reference Exposure Level (REL) dated March 1999, the Dick et al. (1992) and Nelson et al. (1943) studies are contradictory. The former identified a 4-hour NOAEL for irritation and neurobehavioral effects of 200 ppm while the latter reported a 3-minute LOAEL of 200 ppm for irritation.
The California REL for methyl ethyl ketone (MEK) uses the study of Nakaaki (1974), which reports a LOAEL of 270 ppm for "subjective reports of eye, nose, and throat irritation, lacrimation, and sneezing." An uncertainty factor (UF) of 6 was applied to this LOAEL, as was

an interspecies UF of 1 and intraspecies UF of 10 (total UF of 60). Overall, the current CA REL for MEK is 4.5 ppm, or 13 mg/m3. Furthermore, the AEGL-1 based on work of Nelson et al. (1943), which has been characterized as having less accurate MEK measurements and less sophisticated evaluation of irritation than later studies (specifically, Dick et al. 1992 and Nakaaki 1974). Personal communications between CA REL staff and Dick indicates that study should be thrown out as it was not designed to measure irritation thresholds. The Nakaaki (1974) study is not without uncertainty, as the nature of this study (which slowly increased MEK concentrations over a 2-hr period) complicates effort to identify a NOAEL/LOAEL for irritation effects. If it is assumed that the threshold is 100 ppm (from the Nelson study); there should be an intraspecies UF of 10 applied to the selected AEGL-1 threshold value, yielding a new value of 10 ppm. This reviewer suggests using this value of 10 ppm for the 10-, 30-, and 60-minute AEGLs. This would be more in line with risk assessment values from CA, where staff identified a level protective against "severe" adverse effects for a 7-hour exposure to MEK of 11 ppm. This value is nearly an order of magnitude lower than the "mild" effects AEGL-1 value

Response:
The NAC did not find the Dick et al. (1992) and Nelson et al. (1943) studies entirely contradictory. The Dick et al. authors did not find symptoms of irritation at 200 ppm and the Nelson et al. (1943) subjects were willing to tolerate 200 ppm for 8 hours.

As noted, it is important to assess the quality of papers. The Nelson et al. (1943) paper is 60 years old. The exposures were for 3 to 5 minutes. There were no analytical measurements. The study does not meet current standards. It is interesting to note that the paper does state that, "the majority of subjects considered 200 ppm satisfactory for an 8-hour exposure." Where is the "severe" irritation that is being guarded against?
The Nakaaki (1974) paper addressed neurobehavioral effects, and reports of irritation were incidental to the subject of the paper. Even the neurobehavioral study was not a standard one and the paper is dated compared to recent well-conducted studies. As the commenter notes, the exposures in the Nakaaki paper were not constant, but increased over time. Different neurobehavioral results were reported for several other solvents tested in the study (neurobehavioral changes are similar for most solvents). Sensory symptoms are noted, but specific sensory symptoms were not related to specific concentration. But, more troubling is the fact that these symptoms of sensory irritation are NOT REPORTED IN ANY OTHER PAPER... when exposures were to similar concentrations. Therefore, these results must be viewed as questionable.

The Dick et al. studies (1984, 1988, 1992) are well conducted and used adequate numbers of subjects. To disregard the Dick studies because they do not address the threshold for irritation is ludicrous (the Nakaaki 1974 paper also did not address the threshold for sensory irritation). The Dick et al. studies do address subjective symptoms and add to the weight of evidence that 200 ppm is not an irritating concentration. However, additional recent papers that have been added to the MEK TSD may be more suitable as the key

study for the AEGL-1 (see revised TSD).

Toxicologists who do risk assessments should be familiar with the physical and chemical properties of chemicals as well as the mechanism of action. Solvents are not irritants until concentrations of several thousand ppm are reached. Evidence for this is seen in the mouse RD_{50} tests in which concentrations of 9000 to 30,000 were measured or projected as the RD_{50}. MEK has a strong, but not necessarily unpleasant, odor. Odor does not constitute a material health impairment. The concentration of 4.5 ppm (or 10 ppm) would not be defensible for emergency situations in light of the current studies which show no irritation at 200 ppm. Even individuals with self-reported multiple chemical sensitivity did not find concentrations that ranged up to 380 ppm irritating (Seeber et al. 2002). These individuals reported no irritation when tested at 10 ppm.

It should be noted that the AEGL-1 value is lower than many workplace standards which are protective of irritation under repeated or chronic work conditions. The AEGL-1 of 100 ppm is below the 200 ppm of the ACGIH TLV-TWA , OSHA and NIOSH PELs, and German and Dutch workplace standards. The commenter is suggesting that a value that is 1/20th of these standards should be used *under emergency conditions*. Is the commenter suggesting that the California acute RfD should take precedence over the long-established workplace guidelines for chronic exposures?

Comment:
AEGL-2 value:
It is unclear to this reviewer why neurological endpoints were used when it appears fairly clear that the most sensitive endpoint for MEK toxicity is developmental (specifically, the mild fetotoxicity seen from the experiments of Schwetz, Deacon and Mast). Schwetz et al. (1974) identified a LOAEL for lowered birth rats - pregnant rats exposed to 1,000 ppm MEK for 7 hrs/day on days 6-15 of gestation showed statistically significant lower birth weight, shorter rump length, and greater incidence of skeletal abnormalities among pups. This experiment was repeated by Deacon et al. (1981), who added another exposure category, and the results indicated a reproductive LOAEL among rats of 3,000 ppm. Later, Schwetz et al. (1991) repeated the same study using mice instead of rats and these results indicated reproductive LOAEL in mice of 3,000 ppm. The totality of this evidence points indicates that the LOAEL for reproductive effects is likely 3,000 ppm among murine test animals.
Based on these same reproductive toxicity studies, CA REL staff identified a level protective against severe adverse effects for a 7-hour exposure to MEK: 11 ppm (which is 2 full orders of magnitude lower than the proposed AEGL-2 of 1700 ppm. According to HSDB, workers exposed to 300-500 ppm complained of headache, irritation and nausea. Furthermore, two other occupational exposures that involved exposure to MEK in the range of 398 to 561 ppm and acetone in the range of 330 to 495 ppm complained of stomach distress, watery eyes, and headache while conscious; both employees either fainted or were found unconscious following exposure. Unless there is a significant synergism with acetone (such as seen with concurrent

exposures to MEK and n-hexane), this "disabling" (i.e. unconsciousness) effect of MEK inhalation exposure is considerably less than the proposed 1700 ppm AEGL-2. In fact, having unconsciousness (in essence, an impaired ability to escape) result from exposures of "only" 400-600 ppm seems to strengthen the argument to use an intraspecies uncertainty factor of 10 to account for individual variation in response.

Principal studies used by EPA to set the RfC are those done by Schwetz et al. (1991) and Mast et al. (1989); these are considered "one single study," according to EPA's IRIS database. These studies identified a LOAEL of 3020 ppm and NOAEL of 1126 ppm, based on an endpoint of mild, but significant, developmental toxicity in exposed pregnant mice. In addition, they had "medium confidence" in this principal study and thus, assigned uncertainty factors of 10 for interspecies extrapolation, intraspecies sensitivity, and incomplete database (lack of chronic and reproductive toxicity studies). An additional modifying factor of 3 was applied for lack of data on respiratory tract effects for a total uncertainty factor of 3000.

This reviewer suggests the use of the LOAEL identified for developmental endpoints along with uncertainty factors of 10 for both intraspecies and interspecies extrapolation. Furthermore, this reviewer suggests using a modifying factor of 3 to account for database insufficiency and uncertainty involved with applying these developmental effects studies to exposures of 10-, 30-, or 60-minutes. This would yield an AEGL-2 value of 100 ppm.

Response:

MEK is clearly not a developmental toxicant. The fetal effects found in the Schwetz et al. (1974) study could not be repeated in the Deacon et al. (1981) study. The slight fetotoxicity observed among litters of rats exposed to 3000 ppm in the Deacon et al. study involved only an increased incidence of minor skeletal variants. These effects such as extra ribs disappear after birth. And, these effects were accompanied by maternal toxicity in the Deacon et al. study. Considering the higher respiratory rate and higher uptake in rats, and considering that rats were exposed for half of their gestation period (10 of 20 days) and the effects were minor and reversible, the suggestion that this might occur during a 0.3% time period in the human gestation period (an 8-hour period in a 270-day human pregnancy) did not seem likely. It is unlikely that an 8-hour exposure would result in a reduced weight gain in humans over the 270-day period.... the sign of maternal toxicity in rats. Therefore, the NAC chose not to use the developmental studies as the AEGL-2 endpoint. Nevertheless, the chosen AEGL-2 value of 1700 ppm is clearly below the repeat 3000 ppm value that was responsible for the observed effect in rats.

The NAC does not disagree with the U.S. EPA concerning the LOAEL and NOAEL in the Schwetz and Mast studies. However, the effects were minor. In addition, the U.S. EPA sets a Reference Dose, i.e., a lifetime exposure for MEK. The NAC sets a one-time, ≤8-hour exposure for emergency conditions. Concerning uncertainty and modifying factors, it has been the consensus of the NAC and their primary reviewer, the National Academy of Sciences, that uncertainty and modifying factors for AEGLs need not be as stringent as for lifetime exposures.

The studies cited by the commenter (HSDB; Smith and Mayers 1944), as noted above, suffer from many shortcomings. They do not hold up in light of recent, well-conducted studies with careful analytical measurements and surveys of symptoms. These recent studies involve exposures of over 100 healthy individuals as well as a dozen individuals with self-reported multiple chemical sensitivity, a group particularly sensitive to solvent exposure (see Table 2 of revised TSD).

Comment:
AEGL-3 value:
Regarding the AEGL-3, both the AEGL draft document and CA REL staff considered the La Belle and Briger (1955) study as the only one pertinent for development of a life-threatening exposure limit; however, there are differences in methodology for further analysis of this data. The AEGL draft document mentions a study by Hansen et al (1992) – which the CA REL staff do not consider – in which there were no deaths in mice exposed to the maximal study concentration of 26,416 ppm for 30 minutes. In contrast, a CA REL document (but not the AEGL draft document) mentions two later statistical studies done on the 1955 data by Kenneth Crump (Crump and Howe, 1983; Crump, 1984), where the BC05, adjusted for one-hour exposure, was determined to be 14,124 ppm. (The BC01 was also found to be 5790 ppm by Crump's retrospective analysis of the 1955 data.) Fowles et al. (1999) also did some later statistical recrunching of the 1955 data (which was mentioned in AEGL draft document but not the CA REL document) and came up with a MLE01 of 7500 ppm. If one compares lethality data from mice and rats, it appears as if concentrations of roughly 8000 ppm will not cause lethality in mice exposed for 4 hours but will cause 50% lethality in rats exposed for 8 hours.
The NIOSH IDLH is set at 3000 ppm; this level is presumably valid for up to 30-minute exposures. This is considerably less than 30-min "lethal" AEGL-3 of 10,000 ppm.
There appears to be sufficient variation in response between animals with regard to the lethality data to argue for using uncertainty factors of 10 for interspecies and extrapolation for all exposure periods (10-minute through 8-hour). This would yield an AEGL-3 value of 1000 ppm for the 10- and 30-minute exposures. The other AEGL-3 values should be recalculated using an assumed interspecies UF of 10 and not 3.

Response:
It has been the experience of the NAC that mice are generally more sensitive to chemical exposure than rats.... presumably due to their small size and higher respiratory rate. That said, the difference in the lethality for these two species in the two cited studies (Pozanni 1959 and LaBelle and Brieger 1955), both quite old, is not a factor of 10; it is at the most, a factor of 2 if either value is time scaled to the other time. The LaBelle and Brieger study is dated, and if more recent studies with longer exposure durations had been available, they might have been used. The 30-minute study of Hansen et al. (1992) is appropriate for the shorter AEGL-3 exposure durations, not only because it is recent and well-conducted, but also because pharmacokinetic data indicate that uptake would not reach steady state during the 30-minute exposure. Tracheally-cannulated mice also survived the exposures

and there was no serious depression of the central nervous system. The study of Zakhari (1977; no deaths at 50,000 ppm for 45 minutes) supports the Hansen et al. (1992) study.

Comments from S.P. Glenn
Clean Channel Association
Pasadena, Texas

Comment:
I am concerned with some of the AEGL values recommended by the AEGL Committee as they approach the Lower Explosive Level (LEL). The emergency response community has used 10% LEL as their action levels for many years. This safety margin takes into account the error of the instruments and the conditions under which these measurements are taken. The Incident Commander is reminded to re-evaluate any response actions that entry team members would take when levels are above the action level; using higher levels may place teams in dangerous environments without considering other options.

I request the committee remove any value from the summary tables that are above 50% of the LEL. This will prevent emergency responders from erroneously assuming that these levels would not have potential lethal results. When derived values are above 50% of the LEL, the recommended numbers should not be within the summary tables but instead put in a footnote. Levels above 10% of the LEL can be within the tables with a footnote similar to that used for some of the published chemicals.

Both Methyl Ethyl Ketone (MEK) and Xylene have this situation. MEK's 10 and 30-minute values are half the 18,000 ppm LEL. I request the committee put these values in a note below the table. The AEGL-3 values for 1 hour (4,000 ppm) and 4 and 8 hours (both 2,500 ppm) are above 10% of the LEL for MEK. I request that committee mention this in a footnote in the summary tables.

For Xylene, the 10-minute AEGL-3 value of 2,100 ppm is above 10% of the LEL for all forms of Xylene (oxylene (9,000 ppm) and m-and p-xylene LEL (11,000 ppm)) and should be noted in all summary tables. Since the other AEGL 3 values are between 10% of the LEL for o-xylene and m-and p-xylene (11,000 ppm) an additional note should be added to enable emergency responders to draw their own conclusions.

Response:
The original TSD on methyl ethyl ketone was written several years ago. Since that time, the NAC approved adding notations to the Summary Table when the 10 or 50% LEL for a chemical is exceeded. Notations concerning exceedence of the 10 and 50% LEL have been added to the AEGL-3 values in the Summary Table of the revised document.

Reconsideration of
ACUTE EXPOSURE GUIDELINE LEVELS
for
METHYL ETHYL KETONE

National Advisory Committee for AEGLs Meeting 31
December 10-12, 2003

ORNL Staff Scientist:
Sylvia S. Talmage

Chemical Manager:
Bill Bress

Chemical Reviewer:
Loren Koller

METHYL ETHYL KETONE

Reconsideration of AEGL-1

Present AEGL-1 is 100 ppm
- based on Nelson et al. (1943) study of 3-5 minutes duration with no analytical measurements + Dick et al. 1992

Consider raising AEGL-1 to 200 ppm
- Solvents are not irritants

Recent, well-conducted studies:
- Dick et al. (1992) ... 24 subjects
  - 200 ppm for 4 hours
    - odor unobjectionable
    - no subjective symptoms
- Shibata et al. (2002)... 4 subjects, with exercise
  - 200 ppm for 2 hours
    - noticeable odor
    - no irritation, no subjective symptoms

- Muttray et al. (2002)... 19 subjects
  - 200 ppm for 4 hours
    - strong odor
    - no irritation
- Seeber et al. (2002)... 24 subjects (12 MCSs)
  - 10-380 ppm for 4 hours
  - (five 8-minute peaks to 380 ppm)
  - odor was clearly distinguished from irritation
    - intense odor
    - irritation rated "not at all" - healthy subjects
      - "hardly at all" MCS subjects
- Metabolism studies with routine exposures to 200, 300, or 400 ppm, some with exercise

METHYL ETHYL KETONE

Re-wording of AEGL-3 for 10 and 30 minutes

Based on ***projected*** 30-minute mouse RD_{50} of 31,426 ppm (Hansen et al. 1992)
- This concentration was ***not*** actually tested
- The highest tested concentration was 26,416 ppm - no deaths

Supported by rat 30-minute non-lethal concentration of 92,239 ppm (Klimisch 1988)

Suggestion: Keep the 10- and 30-minute AEGL-3 values at 10,000 ppm. Use the Klimisch 1988 study as the basis, with inter- and intraspecies uncertainty factors of 3 and 3, respectively. Use the Hansen et al 1992 study (26,416 ppm) as support with inter- and intraspecies uncertainty factors of 1 (mouse more sensitive) and 3, respectively. Also supported by no deaths in mice exposed to 50,000 ppm for 45 minutes (Zakhari 1977).

METHYL ETHYL KETONE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	*200 ppm*	*200 ppm*	*200 ppm*	*200 ppm*	*200 ppm*
AEGL-2	1700 ppm	1700 ppm	1700 ppm	1700 ppm	1700 ppm
AEGL-3*	10,000 ppm	10,000 ppm	4000 ppm	2500 ppm	2500 ppm

* All AEGL-3 values footnoted for explosive limits.

METHYL ETHYL KETONE AEGLs

Suggestion for AEGL-2:
Flatline the present AEGL-2 value at 1, 4 and 8 hours only (no data for 1-hour value).

At low concentrations of 200 and 400 ppm, MEK approaches steady-state in the blood of human subjects by 3 hours (Liira et al. 1990a). At higher concentrations, steady state takes longer. The data show that higher exposures can be tolerated at the shorter time periods for a common endpoint. The AEGL-2 was based on the threshold for narcosis in a subchronic study with the rat.... 5000 ppm, 6 hours/day, for 90 days (Cavender et al. 1983).

For example, a concentration of 10,000 ppm for 30 minutes did not induce narcosis in the mouse, a more sensitive species than the rat (Hansen et al. 1992). At 10,000 ppm, rats were more active than controls during the first 10 minutes of exposure (Altenkirch et al. 1978a). The concentration of 10,000 ppm is strongly irritating to humans (Patty et al. 1935), but dividing the 10,000 ppm concentration by an intraspecies uncertainty factor of 3 results in 3300 ppm, a concentration with only moderate irritation, and thus within the definition of the AEGL-2.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	3300 ppm	3300 ppm	1700 ppm	1700 ppm	1700 ppm

OR: time scale back from the 4-hour exposure using the default value of n = 3.

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-2	4900 ppm	3400 ppm	2700 ppm	1700 ppm	1700 ppm

METHYL ETHYL KETONE AEGLs

Classification	Exposure Duration				
	10-Minute	30-Minute	1-Hour	4-Hour	8-Hour
AEGL-1	200 ppm	200 ppm	200 ppm	200 ppm	200 ppm
AEGL-2	4900 ppm	3400 ppm	2700 ppm	1700 ppm	1700 ppm
AEGL-3*	10,000 ppm	10,000 ppm	4000 ppm	2500 ppm	2500 ppm

* All AEGL-3 values footnoted for explosive limits.

The AEGL-2 values for 10 and 30 minutes and 1 hour would be footnoted as exceeding 1/10th of the LEL (LEL = 18,000 ppm).

December 10, 2003

ACRYLIC ACID AEGL-2 REVISIT AND DIRECTIONS FOR NAS-13 MEETING IN JANUARY 28, 2004.

HISTORY OF ACRYLIC ACID AEGL-2

FR PUBLICATION MAY 5, 2001 (**30-30-20-9.4-6.4**)
- POD
  - rat
  - 6 hrs
  - 75 ppm
  - Total UF = 10

INTERIM AT NAC-24 ON APRIL 9, 2002 (BALLOT **68-68-46-21-14**)
- POD
  - monkey/rat
  - 3 hrs
  - 75 ppm
  - Total UF = 3

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PRESENTED TO NAS-11 ON JANUARY 27, 2003 (**100-100-68-31-21**)
- POD
  - monkey/rat
  - 6 hrs
  - 75 ppm
  - Total UF = 3

DISCUSSED AT NAC-30 ON SEPTEMBER 16, 2003 IN RESPONSE TO NAS-11 COMMENTS (**100-100-68-31-21**)
- POD
  - monkey/rat
  - 6 hrs
  - 75 ppm
  - Total UF = 3

KEY STUDIES DISCUSSED FOR THE AEGL-2

MONKEYS (Rohm and Haas Co., 1995; Harkema, 2001; Harkema et al., 1997)

Single exposure to 75 ppm for 3 and 6 hours

3 hour exposure = 20 % of olfactory epithelium had acrylic acid induced damage
6 hour exposure = 40-60% of olfactory epithelium had acrylic acid induced damage

Nasal lesions were restricted to the olfactory epithelium lining the dorsal medial meatus at the level of the maxillary sinus in the proximal aspect of both nasal passages. The morphologic alterations consistently found in all acrylic acid-exposed monkeys were focal degeneration and necrosis of the olfactory epithelium with mild inflammation (influx of neutrophils and lymphocytes)

The extent and severity of the lesions were slightly greater in monkeys exposed for 6 hours compared to those exposed for 3 hours. The severity of epithelial injury ranged from mild apical blebbing and cytoplasmic vacuolation of the olfactory sustentacular cells to marked necrosis, exfoliation and attenuation of the olfactory epithelium with only a few remaining basal or sensory cells attached to the basement membrane.

Approximately 20 % and 40-60 % of the olfactory epithelium in the examined sections had acrylic acid induced damage after 3 or 6 hours, respectively. The author concluded that monkeys exposed to acrylic acid had focal, olfactory epithelial lesions that resembled in both nature and severity those reported in rodents.

RATS (Frederick et al., 1998)

Single exposure to 75 ppm for 3 and 6 hours
Harkema (2001) concluded that monkeys exposed to acrylic acid had focal, olfactory epithelial lesions that resembled in both nature and severity those reported in rodents.

WHY WAS 3 HOURS CHOSEN FOR THE POD RATHER THAN 6 HOURS IN NAC-24?

The 3 hour duration was suggested as a middle way. There was no formal discussion of 3 vs 6 hours. There was discussion of uncertainties about which animals were experimental and which were control. Especially in light of some respiratory difficulty seen in one animal. This uncertainty was cited as further support for using 3 vs 6 hours for the POD. However, closer inspection of the Rohm and Haas study indicates that the monkey experiencing respiratory difficulty was in the ethyl acrylate exposed group, not the acrylic acid exposed group.

WHY WAS 68 PPM CHOSEN FOR BOTH THE 30 AND 10 MINUTE VALUES WHEN THE 3 HOUR STUDY WAS USED FOR THE POD IN NAC-24?

Since 75 ppm was the highest dose in monkeys for which data existed, and since rabbits experienced blepharospasm at 129 ppm but not at 77 ppm, the committee was uncomfortable allowing exposures over 75 ppm. For that reason, the 68 ppm value for the 30 minute duration was used for the 10 minute exposure.

Multiple exposure developmental toxicity studies with results observed during first exposure

Species	ppm	Duration	Effect	Reference
rabbit	129	6 hr	blepharospasm	Neeper-Bradley et al., 1997
rabbit	77	6 hr	no blepharospasm	
rat	439	6 hr	eyelid closure & considerable discharge from eyes and nose	Klimisch and Hellwig, 1991
rat	218	6 hr	eyelid closure & discharge from eyes, slightly reddened nose	
rat	114	6 hr	no signs of irritation	
mouse	223		scratching at the nose as a sign of irritation	Miller et al. (1980)
mouse	75		no signs of irritation	

VERBIAGE FROM THE NAC-24 MINUTES

With regard to AEGL-2, the AEGL Development Team considered a level of 75 ppm as an adequate threshold for an AEGL-2 effect because at higher concentrations, clinical effects occurred in animals (tearing and blepharospasm) that could impair the ability to escape, and because olfactory tissue destruction which increases with the exposure concentration is increasingly likely to result in permanent damage of the olfactory epithelium. The available animal data clearly demonstrate that the degree of olfactory epithelium damage increases with increasing exposure time and, thus, argue against using the same exposure concentration as the AEGL-2 value for all relevant periods of time. The AEGL Development Team suggested incorporation of the monkey study into the TSD. This study, together with the histopathological analysis was considered an adequate basis for a further reduction of the interspecies factor to 1. At the same time, this study strengthens the rationale for reduction of the default interspecies factor. For the AEGL-2 derivation, the monkey study will be used as an additional key study. The motion to accept the revised AEGL-2 values was made by Bob Snyder and seconded by Steve Barbee. The motion passed (YES:17; NO:4; Abstain:0) (Appendix F).

SYNOPSIS OF NAS COMMENTS ON AEGL-2 VALUES

1. The Subcommittee is not convinced that histological changes in the olfactory epithelium is the most appropriate endpoint for AEGL-2.

2. The AEGL seems conservative given the relatively subtle changes. COT raises the question whether the olfactory epithelium has the capacity to repair/regenerate.

OPTIONS

1. PRESENT THE ORIGINALLY BALLOTED VALUES TO THE NAS (**68-68-46-21-14**)

   Not consistent with SOP direction on choice of POD effect. The highest exposure not causeing irreversible effects is 6 hours, not 3 hours.

2. RE-BALLOT THE AEGL-2 VALUES TO (**100-100-68-31-21**)

   AEGL-2 values for 10 minutes and 30 minutes exceed the 77 ppm level which did not cause blepharospasm in rabbits. The no effect level for eyelid closure & discharge from eyes in rats is 114 ppm.

3. OTHER?